Relation of C-Reactive Protein and Uric Acid Levels with Microalbuminuria in Type 2 Diabetic Patients

Tip 2 Diyabetik Hastalarda C-Reaktif Protein ve Ürik Asit Seviyeleri ile Mikroalbüminürinin İlişkisi

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ABSTRACT Objective: Microalbuminuria is associated with increased cardiovascular morbidity and mortality in diabetic subjects. C-reactive protein and uric acid are also thought to be associated with cardiovascular events. There are conflicting study results about the relation of C-reactive protein and uric acid with microalbuminuria. We planned to evaluate the relation of C-reactive protein and uric acid with microalbuminuria in type 2 diabetic patients. **Material and Methods:** We recruited a total of 114 type 2 diabetic patients, 44 of them having and 70 of them not having microalbuminuria. After physical examination, their blood were drawn when fasting for fasting plasma glucose, Hb A1c, fasting insulin, serum total and high density lipoprotein cholesterol, triglyceride, creatinine, high sensitive C-reactive protein, uric acid levels and then postprandially for postprandial plasma glucose, afterwards their urine were obtained. We also performed antropometric measurements. Body mass indices, low density lipoprotein cholesterol levels, indirect insulin resistance indices and creatinine clearences were calculated. Then we compared all their parameters including high sensitive C-reactive protein and uric acid levels in our groups; and we made correlation analysis in our diabetic patients. **Results:** We found that only high sensitive C-reactive protein and uric acid levels were significantly high in diabetics with microalbuminuria than without microalbuminuria ($p<0.001$ both). There was positive correlation between microalbuminuria and high sensitive C-reactive protein ($p:<0.05$, $r:0.20$). We did not find a correlation between microalbuminuria and uric acid, but high sensitive C-reactive protein was positively correlated with uric acid ($p:<0.01$, $r:0.25$). **Conclusion:** These results suggests that high sensitive C-reactive protein may be associated with microalbuminuria at least in a small group of Turkish type 2 diabetic patients.

Key Words: Diabetes mellitus, type 2; uric acid; C-reactive protein; albuminuria

ÖZET Amaç: Mikroalbüminüri diyabetik kişilerde artmış kardiyovasküler morbidite ve mortalite ile ilişkilidir. C-reaktif protein ve ürik asidin de kardiyovasküler olaylar ile ilgili olduğu düşünülmektedir. C-reaktif protein ve ürik asit ile mikroalbüminürinin ilişkisi konusunda çelişkili araştırma sonuçları mevcuttur. Biz, tip 2 diyabetik hastalarda C-reaktif protein ve ürik asit ile mikroalbüminüri ilişkisini araştırmayı planladık. **Gereç ve Yöntemler:** Kırk dördü mikroalbüminürili, 70'i mikroalbüminürisiz toplam 114 tip 2 diyabetik hastayı çalışmamıza aldık. Fizik muayeneden sonra aç karnına açlık kan şekeri, Hb A1c, açlık insülini, serum total, düşük ve yüksek dansiteli lipoprotein kolesterol, trigliserid, kreatinin, yüksek hassasiyete sahip C-reaktif protein, ürik asit için ve tok karnına tokluk kan şekeri için hastaların kanları alındı, sonra antropometrik ölçümleri yapıldı, ayrıca idrarları alındı. Daha sonra vücut kitle indeksleri, düşük dansiteli lipoprotein kolesterol ve indirekt insülin rezistans indeksleri ve kreatinin klirensleri hesaplandı. Bunları takiben hastaların tüm parametreleri kıyaslandı ve tüm tip 2 diyabetik hastalarda korelasyon analizi yapıldı. **Bulgular:** Mikroalbüminürili hastalarda, mikroalbüminürisiz olanlarla kıyaslandığında sadece yüksek hassasiyete sahip C-reaktif protein ve ürik asit seviyelerini artmış olarak saptadık ($p<0,001$ her ikisi de). Mikroalbüminüri ve yüksek hassasiyete sahip C-reaktif protein arasında pozitif korelasyon vardı ($p:<0,05$, $r:0,20$). Mikroalbüminüri ve ürik asit arasında korelasyon saptamamamıza rağmen, yüksek hassasiyete sahip C-reaktif protein ürik asit ile pozitif olarak korele idi ($p:<0,01$, $r:0,25$). **Sonuç:** Sonuçlarımız, en azından küçük bir tip 2 diyabetik Türk popülasyonunda C-reaktif protein ile mikroalbüminürinin ilişkili olabileceğini göstermektedir.

Anahtar Kelimeler: Diabetes mellitus, tip 2; ürik asit; C-reaktif protein; albüminüri

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Diabetic nephropathy is the leading cause of end stage renal disease.[1] Microalbuminuria (MA) is considered the best non-invasive test for incipient nephropathy and a good predictor of progression to renal disease.[2] It is also found to be associated with increased cardiovascular mortality and morbidity in type 1 and type 2 diabetic patients.[3-6]

C-reactive protein (CRP) is a very sensitive marker of inflammation. It has been increasingly highlighted as a strong predictor of future cardiovascular events.[7-9]

The role of uric acid (UA) as an independent marker of cardiovascular risk has been controversial for decades. Serum UA levels have been shown to be correlated with negative outcomes in general population and type 2 diabetic subjects.[10-12]

There are conflicting study results about the relation of CRP and UA with MA. In order to search for cardiovascular risk screening strategy, it will be necessary to examine the relationships among established risk factors and new candidates. In this study we investigated the relationship of MA with CRP and UA in patients with type 2 diabetes mellitus (T2DM).

MATERIAL AND METHODS

PATIENTS

In this cross-sectional study a total of 114 T2DM patients, aged from 30-80 years, were recruited from the outpatient Clinic of Ankara Training and Research Hospital from February 2011 to October 2011. Seventy nine of them were female (69.2%), 35 of them were male (30.7%). T2DM was diagnosed according to the criteria of American Diabetes Association 2011. The patients were classified as having microalbuminuria (with 30-300 mg microalbumin in 24 hour urine) and without microalbuminuria (with <30 mg microalbumin in 24 hour urine). Fourty four patients dropped into microalbuminuria (+) group and 70 of them into microalbuminuria (-) group.

The patients did not show a history of diabetic ketoacidosis at the onset of diabetes and none were being treated with insulin and antihypertensive drugs at the time of recruitement. Patients using uric acid lowering agents, diuretics or alcholic beverages were excluded. Patients with acute illness, malignancy, fever or urinary tract infection were likewise excluded. We also did not included patients with glomerular filtration rate <60 mL/min, pregnancy and having diseases that may interfere serum CRP levels.

After detailed physical examination, we measured body weight and height of all the patients. We calculated body mass index (BMI) as weight in kilograms divided by the square of height in meters (kg/m^2).

Blood was withdrawn after 12 hour of overnight fasting, at 08.30 a.m. for fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), fasting insulin (FI), serum total and HDL cholesterol (HDL-C), triglyceride (TG), creatinine, high sensitivity CRP (hsCRP) and uric acid levels. Another blood sample was taken for postprandial plasma glucose (PPPG) 2 h after breakfast.

An indirect measure of insulin resistance was calculated from the fasting plasma insulin (μ unite/mL)xfasting plasma glucose (mmol/l)/22.5 formula as homeostasis model assessment-insulin resistance (HOMA-IR). Creatinine clearance was calculated by the formula of urine creatininexvolum of the urine/serum creatinine x1440.

Systolic and diastolic blood pressure (SBP and DBP) were measured after a 5 min rest in the semi-sitting position with a sphygmomanometer. Blood pressure (BP) was determined at least three times at the right upper arm, and the mean was used in the analysis. Korotkoff's first phase was accepted as systolic and fifth phase was accepted as diastolic pressure.

LABORATORY METHODS

Plasma glucose, uric acid, total cholesterol, TG and HDL-C concentrations were determined by enzymocalorimetric spectrophotometric method in a Roche/Hitachi molecular PP autoanalyser. Low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald Formula (LDL: Total cholesterol-HDL-TG/5). HbA1c was measured by

turbidometric inhibition immunoassay in oto-analyser. FI was measured by TOSOH G7 HPLC system. High sensitivity C-reactive protein (hsCRP) was measured by immunoflowmetric test with Beckman-Cutler device. Microalbuminuria was investigated in 24 s urine by turbidometric method.

METHODS

After comparing all the parameters in two groups of T2DM patients with and without microalbuminuria, we performed correlation analysis between parameters in all our type 2 diabetics.

This study was performed according to the Helsinki decleration 2008. The local ethics commitee approved this study and all the subjects gave written informed consent.

STATISTICAL ANALYSIS

Calculations were performed using SPSS version 12. Student's test and Chi-square test were used to compare the groups. Correlation between variables was calculated by Pearson correlation analysis. Data were presented as mean ± SD. A p value of <0.05 was considered as statistically significant.

RESULTS

We performed the study with 114 T2DM patients. All the demographic and laboratory findings of the patients were presented in Table 1.

When we made correlation analysis in all diabetic patients we found positive correlations between MA and hsCRP (p:<0.05, r:0.20) and HbA1c (p:<0.001, r:0.28) and between hsCRP and uric acid (p:<0.01, r:0.25) and total cholesterol (p:<0.01, r:0.21) and LDL-C (p:<0.01, r:0.22) (Table 2).

DISCUSSION

Chronic low grade inflammation and endothelial dysfunction are proved to play important roles in the development of both micro and macrovascular complications of T2DM. CRP is an acute phase reactant and a sensitive marker of inflammation. It has also been accepted to be a marker of cardiovascular risk.[7-9] Uric acid levels have been linked to cardiovascular and renal diseases, possibly through the generation of reactive oxygen species and subsequent endothelial dysfunction.

In the study where we examined the relation of MA with hsCRP and UA in diabetic patients, we found that hsCRP and UA levels of microalbuminuric type 2 diabetic patients were significantly higher than those levels of non-microalbuminuric ones. We were not able to show any diference in

TABLE 1: Demographic and laboratory findings of type 2 diabetic patients with and without microalbuminuria.

	MA (-) n: 70	MA (+) n: 44	p
Age (year)	56.0±8.3	56.5±11.1	NS
BMI (kg/m^2)	29.1±3.9	29.9±5.6	NS
SBP (mmHg)	128.0±30.7	129.9±25.5	NS
DBP (mmHg)	88.9±10.3	88.0±5.8	NS
FBG (mg/dl)	150.2±63.4	160.1±61.0	NS
PPBG (mg/dl)	230.1±103.7	235.7±91.4	NS
HbA1c (%)	7.6±1.8	8.2±2.4	NS
FI (µU/ ml)	8.9±5.8	8.5±4.9	NS
HOMA-IR	3.8±2.5	3.2±2.5	NS
T.Chol. (mg/dl)	196.8±43.2	208.0±43.1	NS
LDL-C (mg/dl)	119.1±35.2	121.7±32.3	NS
HDL-C (mg/dl)	44.8±10.0	46.7±8.7	NS
TG (mg/dl)	171.3±100.9	195.2±110.5	NS
Cr. Cl. (ml/min)	124.3±49.6	129.3±55.5	NS
UA (mg/dl)	4.5±1.1	5.3±1.7	<0.001
hsCRP (mg/dl)	3.3±2.5	5.6±2.8	<0.001

MA: Microalbuminuria; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; PPBG: Post prandial blood glucose; HbA1c: Hemoglobin A1c; FI: Fasting insulin; HOMA-IR: Homeostasis model assesment index-insulin resistance; T. Chol: Total cholesterol; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; TG: Triglyceride; Cr. Cl: Creatinine clearance; UA: Uric acid; hsCRP: High sensitivity C-reactive protein. Data were presented as mean ± SD. NS: Nonsignificant.

TABLE 2: Positive correlations in correlation analysis of all diabetic patients.

	hsCRP	MA	UA
hsCRP		p:<0.05, r:0.20	p:<0.01, r:0.25
HbA1c	p:<0.001, r:0.28		
T. Chol	p:<0.01, r:0.21		
LDL-C	p:<0.01, r:0.22		

MA: Microalbuminuria; HbA1c: Hemoglobin A1c; T.Chol: Total cholesterol; LDL-C: Low density lipoprotein cholesterol; UA: Uric acid.

another demographic finding of patients with and without MA. We thought that the reason of it were the exclusion criteria; we recruited the patients who had not severe diabetes and had less complications. We also determined that hsCRP levels of our patients were positively correlated with microalbuminuria, but although hsCRP and UA levels were positively correlated we could not be able to show positive correlation between MA and UA.

In most of the studies, but not in all, hsCRP is thought to be associated with microalbuminuria in T2DM patients.[13-21] MA was also found to be accompanied with incraesed hsCRP levels in patients without diabetes.[22-25] As we found that hsCRP levels were higher in our type 2 diabetic patients with microalbuminuria than without microlabuminuria, our findings suggest that low grade inflammation as assessed by hsCRP may play some role in the development of microalbuminuria. Furthermore, it was reported that hsCRP may increase adhesion molecular expression and decrease the production of nitric oxide and potentiate endothelial dysfunction.[26,27] Elevated levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase, together with increased hsCRP levels were found to be associated with microalbuminuria in untreated hypertensive patients.[24] It may be reasonable to speculate that hsCRP is related to the development of diabetic nephropathy.

In the study of Fu et al. the prevalance rate of MA was found to be increased progressively with increasing levels of hsCRP from the lowest to the highest quartile.[19] In Tsioufis et al. study stratification based on hsCRP level showed that MA was higher in patients with hypertension in the highest hsCRP levels.[24] In concordance with them we found positive correlation between hsCRP and MA. As hsCRP is an easy test, we think that it will be wise to recommend to examine hsCRP in T2DM patients in order to strengthen the diagnosis of nephropathy in early stages.

Results of the studies about UA, diabetes mellitus and endothelial function are controversial. Increased free radical activity in blood and arterial intima appears to contribute to endothelial dysfunction, which can be ameloriated by administration of antioxidants.[28] In humans, UA is the most abundant aqueous antioxidant, accounting for up to 60% of serum free radical scavenging capacity.[29] Serum UA levels were found to be reduced in type 1 diabetic patients, possibly because of high uric acid renal clearence.[30] In T1DM patients receiving 1000 mg uric acid intravenously, improved endothelial function in the forearm vascular bed was shown, suggesting that high UA concentrations in vivo may serve a protective role in conditions associated with increased cardiovascular risk.[31] We think that this acute effect of UA in so small number of patients, that was eight; needs further examination. Bo et al. in their study concluded that in T2DM, hypouricemia was associated with worse metabolic control, hyperfiltration and a late onset or decreased progression to overt nephropathy, while hyperuricemia seemed to be associated with the insulin resistant syndrome and with early onset or increased progression to overt nephropathy.[32]

Studies have identified a strong association between raised serum UA concentrations and increased cardiovascular risk as well as renal disease. However disagreement still exists over whether UA level is simply a marker or by itself is a contributory factor to the microvascular disease and nephropathy in diabetes.[10-12] Epidemiological studies have found that hyperuricemia was an independent risk factor for renal dysfunction in general population, in patients with hypertension.[33-35] In animal models, elevated level of uric acid can lead to arteriolopathy of preglomerular vessels, impaired autoregulation, glomerular hypertension, as well as endothelial dysfunction. Evidence of UA as an important player in the development of kidney disease independently of blood pressure or deposition of uric acid crystals, probably by inducing oxidative stress or by involving the renin-angiotensin system in diabetes is convincing and well found based on animal data.[36-39]

In human beings effect of UA in both the initiation and progression of diabetic kidney disease has recently been evaluated. In a study from the Steno Diabetes Center, where T1DM patients were

followed up for 18 years, the mean level of serum UA was significantly higher in patients who eventually progressed to overt diabetic nephropathy, that is, persistent macroalbuminuria versus those who remained normoalbuminuric or who later progressed to microalbuminuria only.[40] In a recent study, Jalal et al. confirmed these findings by showing that serum UA was a strong predictor of the development of albuminuria in patients with T1DM in a study of 324 patients who were followed up for 6 years.[41] Serum UA concentration was also found to be associated with MA in men with T2DM.[42] A dose-response relationship between serum UA and MA has recently been demonstrated in patients with type 1 diabetes and type 2 diabetes.[43,44] Trials on drugs that lower uric acid were reported to reduce the severity of renal disease and proteinuria in T2DM.[45-47] In our study we also found that UA levels of our patients with MA were statistically higher than the patients without MA. It was interesting that we were not able to find positive correlation between MA and UA. However our study demonstrated a positive correlation between serum UA and hsCRP levels as reported by an other study.[19,48] The reason why we could not show positive correlation between MA and UA levels may be the small size of our groups.

Compared with normoglycemic subjects, T2DM patients or subjects with impaired glucose regulation had significantly higher serum CRP concentration in men and women.[49] This relation was also demonstrated in healthy subjects.[50] Like our study correlation with CRP and HbA1c was demonstrated.[51,52] Recent studies have also demonstrated a close relationship between elevated CRP and plasma lipids.[53-55] Several authors have also shown that in addition to lowering LDL-C, statins also lower CRP.[56,57] In our study we demonstrated a positive correation with hsCRP and LDL-C.

Limitations of this study include its cross-sectional nature in a single center and lack of generalizability to Turkish population. We did not consider statin therapy which was known to have anti-inflammatory properties in comparing the parameters. Additionaly, enlargement of sizes of the groups are needed.

Despite the aforementioned limitations of our study, in conclusion, hsCRP levels were related to microalbuminuria in type 2 diabetic patients. We speculate whether we can use hsCRP when evaluating nephropathy in diabetic patients.

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